Safety, tolerability, and clinical effects of ZP8396, a novel long-acting amylin analog: A single ascending dose trial

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INTRODUCTION

ZP8396 is a long-acting amylin analog designed for once-weekly dosing that has demonstrated the potential to reduce body weight and improve glycemia in animal models of obesity and diabetes

OBJECTIVES & ENDPOINTS

Objectives

- A first-in-human trial to evaluate safety, tolerability, pharmaco-kinetics (PK), and pharmacodynamics (PD) of ZP8396

Primary Endpoint

- Adverse events (AEs)

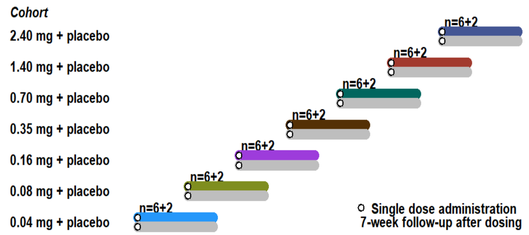
Secondary Endpoints

- PK parameters of ZP8396 and PD parameters in relation to a Mixed Test Meal (MTM)

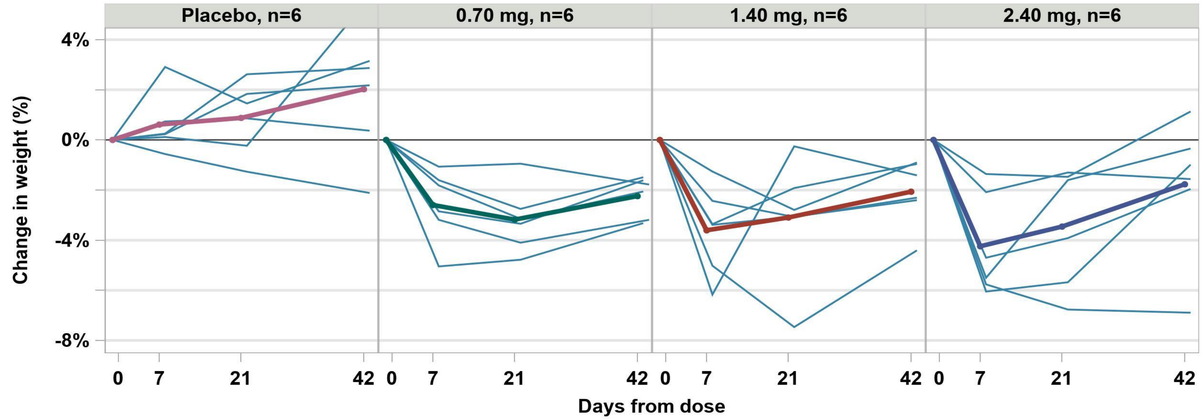
METHODS

- A randomized, double-blind, placebo-controlled trial was performed to assess safety, PK, and PD of a single subcutaneous injection of ZP8396 in healthy, lean and overweight male subjects
- A total of 56 subjects (mean age 38.1 years; mean BMI 25.6 kg/m^2) were randomized to ZP8396 or placebo (6:2) within seven dose cohorts ranging from 0.04 to 2.4 mg

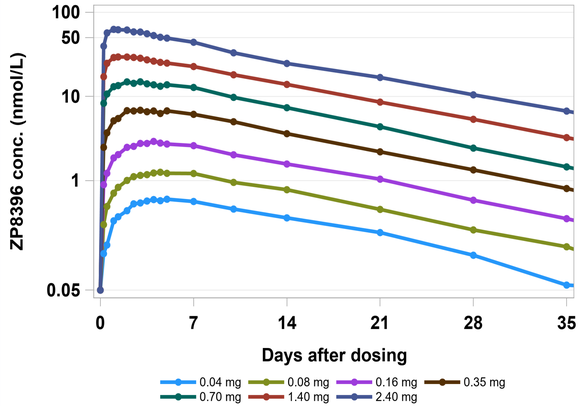
TRIAL DESIGN



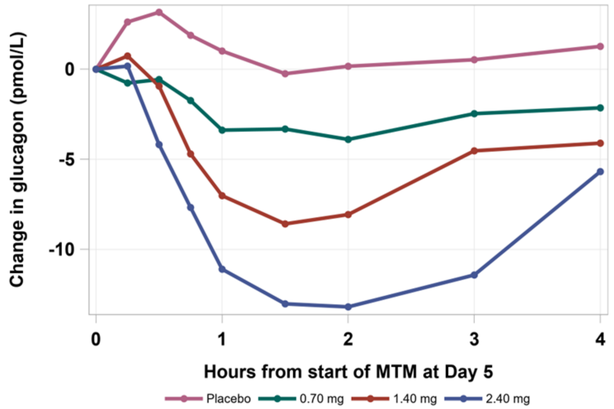
DOSE-DEPENDENT AND CONSISTENT WEIGHT LOSS



MEAN HALF-LIFE OF 10 DAYS



DOSE RESPONSE IN GLUCAGON SECRETION



TREATMENT EMERGENT ADVERSE EVENTS (TEAEs)

No. of subjects (events)	Placebo n=14	0.04 mg n=6	0.08 mg n=6	0.16 mg n=6	0.35 mg n=6	0.70 mg n=6	1.40 mg n=6	2.40 mg n=6
Total AEs	10 (15)	3 (5)	3 (7)	2 (3)	1 (3)	5 (11)	6 (23)	6 (27)
Mild AEs	8 (8)	3 (3)	3 (6)	1 (2)	1 (3)	5 (10)	6 (18)	6 (16)
Moderate AEs	5 (7)	2 (2)	1 (1)	1 (1)	0	1 (1)	5 (5)	5 (11)
Severe AEs	0	0	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0	0	0
Gastrointestinal disorders AEs	0	0	1 (2)	0	1 (1)	2 (2)	5 (9)	5 (12)
Metabolism and nutrition disorders AEs	0	0	0	0	0	2 (2)	5 (5)	6 (8)

RESULTS

- After 7 days observation, mean body weight decreased by -0.6%, 2.6%, 3.6%, and 4.2% from baseline following a single dose of placebo, 0.7, 1.4 and 2.4 mg, respectively
- ZP8396 was well tolerated, with no serious or severe TEAEs and no withdrawals
- Most common related TEAEs were decreased appetite, nausea and vomiting, most events were mild and transient. Nausea and vomiting only occurred in two highest dose groups
- Number and severity of gastrointestinal TEAEs increased with dose
- The mean half-life of ZP8396 was approximately 10 days
- Dose-dependent reduction in glucagon release was observed
- No anti-drug antibodies were detected

CONCLUSIONS

- ZP8396 was well-tolerated in single doses of up to 2.4 mg
- A half-life of approximately 10 days is suitable for once weekly dosing
- A single dose of ZP8396 resulted in a dose-dependent, consistent and sustained reduction in body weight, supporting the potential as a treatment for obesity
- The first part of MAD (Multiple Ascending Dose) trial results will be released in later half of 2023